Movement Disorders
CLINICAL PRACTICE
REVIEW

# *Banisteriopsis caapi*, a Forgotten Potential Therapy for Parkinson's Disease?

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**Abstract:** *Banisteriopsis caapi*, a liana indigenous to the Amazon basin with metagnomigenic properties and possible anti-depressant effects is one of the natural sources of harmala alkaloids. A summary of early trials with extracts of *Banisteriopsis caapi* and *Peganum harmala* (from which harmine was first isolated) in the 1920s and 1930s on various forms of parkinsonism is given as well as a brief overview of the known pharmacological properties of harmine. Despite its earlier abandonment because of perceived weaker efficacy than solanaceous alkaloids like scopolamine and hyoscine we propose that harmine should be reconsidered as a potential rapidly acting anti-Parkinsonian agent.

Harmine, or methoxyharman, also formerly known as banisterine, telepathine, and yageine, is a beta carboline, which along with harmaline (tetra hydro harmine) was first isolated from the seed pots of the Syrian rue *Peganum harmala* (*P. harmala*) (Fig. 1). Native to North Africa and the Middle East, this drought-resistant perennial with white flowers and spiky leaves has seeds that fluorescence yellow in water. Incense prepared from its dried capsules has been claimed, in the Koran, to protect against the evil eye. As long ago as 1626, Matthioulos drew attention to its value as a treatment for "melancholy" and it has also been considered to have intoxicant properties.[1] Harmine and harmaline are also found in considerable quantities in the tobacco plant, passion flower and lemon balm plants, and in the wings of several Nymphalid butterflies.

On the opposite side of the world, in the jungles of South America, a concoction (yagé, ayahuasca, or hoasca) prepared from scrapings of *Banisteriopsis caapi* (*B. caapi*) liana mixed with leaves of *Psychotropa viridis* has been used for centuries by the indigenous tribes of the Amazon as an entheogen.[2] The "vine of the soul" (Fig. 1) was first identified as a hallucinogen by Richard Spruce during his plant hunting expeditions to South America in 1852, where he observed its use as a potion by the shamans to induce time traveling and clairvoyance.

In 1905, the Colombian naturalist and pharmaceutical chemist, Rafael Zerda Bayón, administered a preparation of "yagé" to a soldier far from home who reported visions of his sister's death, which was tragically confirmed by letter to him a few weeks later. Convinced of yagé's mind expanding powers, Zerda Bayón suggested the alternative rubric of "telepathine," a name that was retained when the active alkaloid was first isolated in 1923 by another Columbian chemist, Guillermo Fischer Cárdenas. In 1925, Barriga Villalba, professor of chemistry at the University of Bogotá, crystallized some samples of *B. caapi* and named the active substance "yagéine." In collaboration with Hoffmann-La Roche (Basel, Switzerland), Elger, and the pharmacist Robinson, isolated the alkaloid and demonstrated that telepathine and yagé were both identical to harmine.[3]

Another pharmaceutical company, E. Merck (Darmstadt, Germany), was also interested in the medicinal potential of phantasticants such as mescaline and received a large quantity of yagé in 1926 from Colombia. By 1927, they had stockpiled 30 kg of *B. caapi* extract and 2,000 kg of *P. harmala*. At that time, it was still thought that these two plants had different pharmacological properties, but in 1928, harmine was shown to be the active alkaloid in both plants.[4]

Eduard Merck asked Louis Lewin (1850–1929), a prominent pharmacologist and medical doctor who worked in Berlin and who devised a systemic classification of psychoactive plants and synthetic drugs based on their pharmacological properties for help to analyze the haramala alkaloids.[3] In view of his previous successful collaboration with the company in relation to mescaline, Lewin was offered a consultancy to further investigate the potential of "the devil's vine" (*B. caapi*) as a medicine. In 1888, Lewin, who had self-experimented with mescaline in his private

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**Figure 1** *Banisteriopsis caapi* (left) and *Peganum harmala* (right).

apartment, was unable to publish his findings because of limited supplies and therefore approached Merck for assistance. This collaboration led to several publications, and a variant of the peyote cactus was named *Anhalonium lewinii* in recognition of his research.

From the samples of *B. caapi*, Lewin extracted an alkaloid that he named "banisterine," which he then tested on dogs and monkeys. Lewin also described experiments of the ethnologist, Theodor Koch-Gruenberg, who self-administered harmine and reported changes of color perception and mild hallucinations, which, however, did not reach the intensity of mescaline intoxication.[5] He ingested banisterine and felt invigorated and had improved and faster motor control, but did not experience the mind altering state that had been reported by the early travelers in the Amazon. Lewin then administered banisterine subcutaneously (SC) to an obese patient who had hemiplegia who reported immediate improvement in her gait.[5] Encouraged by this response, he then gave SC injections of 25 to 70 mg of banisterine to patients with several different neurological diseases in the Neukoelln Hospital, where some of the patients reported euphoria, warmth, and lightness of the limbs in some cases.[6]

## Use of Harmine in Parkinsonism

Given his observation that *B. caapi* can facilitate movement, Lewin speculated that the drug may be efficacious in patients with paralysis agitans and postencephalitic parkinsonism. He was nearing retirement and suggested that two younger colleagues from Heidelberg, Karl Wilmans and Kurt Beringer, who had also been supplied with *B. caapi* samples by Merck should conduct the first empirical trials.

Although, by 1928, Merck reported that *P. harmala* and *B. caapi* were chemically identical,[4] Lewin, in contrast to Beringer, was convinced that *B. caapi* was superior to the extracts of *P. harmala*. Shortly before his death in December 1929, Lewin presented 3 patients with postencephalitic parkinsonism at the meeting of the Berlin Medical Association, demonstrating a dramatic benefit in neurological handicaps after SC injections of *B. caapi*. He also regarded banisterine as superior to hyoscine in its ability to alleviate rigor.[3] Given his experiments, he asked for further funding from Merck to import more banisterine from South America, but owing to the recent reports that the alkaloid was not a "rare and extremely precious" commodity, but identical to extracts of the much more common *P. harmala*, substance funding was denied.

In early 1929, Beringer, whose major research area had been psychosis and mescaline-induced hallucinations, administered 100 mg of banisterine to a laboratory colleague and noted an "uncontrollable tremor in the arms and legs, similar to what we see in parkinsonian patients." He then treated 15 postencephalitic patients with extracts of *P. harmala* and noted a dramatic improvement in motor signs in some cases (see Video 1). In one 29-year-old patient with severe postencephalitic parkinsonism, a course of *P. harmala* extract (12 drops three times daily) led to a marked improvement in rigidity and oromandibular dystonia with the patient reporting "Doctor, I am healthy again."[7] Beringer concluded that the treatment had the potential of alleviating symptoms of akinesia, rigidity, and oculogyric crisis in patients with postencephalitic parkinsonism and slowness in paralysis agitans. This therapeutic effect was noted to occur after around 30 minutes, but its effect varied and the benefit could last between several hours and a few days.[3]

Merck dedicated the first 19 pages of their "*E. Merck's Jahresbericht ueber Neuerungen auf den Gebieten der Pharmakotherapie und Pharmazie 1928*" to harmine and marketed the drug for postencephalitic parkinsonism and paralysis agitans in late 1928 in capsules, suppository, and as injectable solution form (Fig. 2).


**Figure 2** Harmine for postencephalitic parkinsonism and idiopathic PD was produced by Merck and available as capsules, suppository, and SC injections. Original harmine lyophilized powder and harmine vial for SC injections. Pictures taken at Merck (Darmstadt, Germany).


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Given that extracts of *P. harmala* were easier and more easily procurable, "Merck's harmine" did not contain extracts of *B. caapi*. Decourt and Lemaine reported that "Merck's harmine" was mainly effective in young patients with postencephalitic parkinsonism without tremor. They also reported that, when taken orally, the drug lost most of its efficacy, whereas Beringer noted good effects when it was administered in keratinized capsules.

Frank and Schlesinger also stated very good effect in 80% of their patients with postencephalitic parkinsonism. Bradykinesia, drooling, hypomimia, gait, and postural stability improved in 10 of 12 patients. Furthermore, mood improved considerably, and in 1 case euphoria ensued (a patient who was unable to move made a handstand in the hospital); in others, pre-existing anger and aggressive behavior worsened. Tremor was not improved.[8] In their study, parkinsonian symptoms improved within 15 minutes after SC injections and took approximately 20 minutes when administered orally. The duration of the effect lasted between 3 and 5 hours and 3 and 4 days. Often, motor handicap only lessened after repetitive administration of banisterine, but in some, parkinsonism improved after the first dose. The average daily dose, which was used for injections, was 20 and 40 mg/day when orally administered. Side effects usually occurred at higher doses (60 mg) and included yawning, nausea, vertigo, headache, agitation, tinnitus, bradycardia, and orthostatic dysregulation.

Schuster treated 18 patients with paralysis agitans and "*similar striatal lesions*" with SC banisterine, with doses ranging between 20 and 40 mg. After 15 minutes, he noted improvement on rigidity with only minimal side effects, such as nausea and occasional vomiting. Effects were lasting for 2 to 6 hours and in some up to 7 days.[1] However, effects only lasted for a few hours, and therefore Schuster and Lewin tried to extend the effect of banisterine and "Merck's harmine" by constriction of the jugular vein.[3]

A number of other German centers also reported spectacular results with "Merck's harmine" (see Table 1). "Merck's harmine" was used with success in patients with postencephalitic parkinsonism, paralysis agitans, and pallidal rigidity, but also in patients with carbon monoxide poisoning as well as in those with arteriosclerotic rigidity.[3]

Ernst Rustige received 27 injections from Merck (3—50 mg) to treat 18 patients and also capsules (3 × 10 mg per day) for 2 patients. He noted a general improvement of motor function with increased speed of movement in 13 patients. In 6 patients rigidity improved, and in 3 of these patients the pronounced rigidity disappeared completely. An objective improvement was observed after 20 to 30 minutes and the effects lasted for a maximum of 1 hour. In 9 patients "Merck's harmine" had a variable effect on tremor with improvement in some, but also worsening in others. Only 4 of the 18 patients did not show any benefit at all from harmine injections.[1] Rustige also injected saline in some patients and reported that only 1 control patient reported improvement, whereas all others reported no effect. However, he also noted that "these patients were pleased, unfortunately overly pleased, with the new agent which would now help them." They repeatedly showed other patients with pride everything of which they were now capable and were disappointed over the rapid decline of the effect.[3] In 1931, Mueller reported that harmine has been successfully used in all extrapyramidal disorders at Nonne's clinic for the last year and a half. Patients were administered SC injections of harmine in the morning in combination with "Merck's keratinized capsules" at midday for a period of 3 to 4 weeks. They reported that excellent improvement was achieved in 26% of patients and good improvement in 37%.[3]

However, by late 1929, Beringer was already aware of the unrealistic expectations for the drug and emphasized in his presentations that the effects were variable and short lasting and stated that "aroused hopes in the ill could not be fulfilled." He also warned about the "exaggerated and extravagant reports in the newspapers," which, in his opinion, were unrealistic and would lead to patient disappointment. Furthermore, the SC administration of "Mercks harmine" or banisterine, which appeared to be the most effective route of administration, was not suitable for all patients. "Meck's harmine suppositories" were found to be efficacious only in a minority of patients. Although Beringer treated some patients with infusions of Peganum extract and noted alleviation of tremor, he suggested that atropine and scopolamine may be more suitable given that their effects were more predictable than harmine. He wrote that: "The brilliant successes are currently a minority and are matched by an equal number of complete treatment failures. In

**TABLE 1** Summary of studies performed with banisterine/harmine in patients with parkinsonism between 1928 and 1931

| Symptoms | No. of Patients | Efficacy | Authors |
|---|---|---|---|
| PEP | 15 | +++ | Beringer[a] |
| PEP | 30 | ++ | Rosenberger |
| Parkinsonism | 4 | +++ | Frank, Schlesinger |
| | 4 | ++ | |
| | 2 | + | |
| | 2 | – | |
| PD, chorea minor | 2 | – | |
| | 2 | — | |
| PEP | 1 | +++ | Fischer |
| | 2 | ++ | |
| PEP | 7 | ++ | Schuster |
| PD | 7 | ++ | |
| PEP | 2 | – | |
| $CO_2$ poisoning | 1 | – | |
| Self-experiment | 1 | | |
| PEP | 13 | ++ | Pineas |
| Parkinson's disease | 5 | + | |
| PEP | 20 | ++ | Rustige |
| PEP | 37 | – | Hill, Worster-Drought |
| | 1 | +/– | |
| PEP | 8 | +/– | Gausebeck |
| | 1 | +++ | |
| PD | 1 | +/– | |
| PEP | 15 | + | Cooper, Gunn |

+++, excellent response; ++, good response; +, mild improvement; +/–, very mild improvement; –, no effect; —, worsening of symptoms. The majority of these patients were treated with SC harmine/banisterine injections, but in a few exceptions, harmine capsules as well as harmine drops were given.
[a]Beringer treated more patients between 1929 and 1931.
PEP, postencephalitic parkinsonism; PD, Parkinson's disease.


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between lie a bulk of cases where only a moderately significant improvement of varying practical and therapeutic degree can be achieved. The reason for this unreliability of the therapeutic effect (. . .) is unknown as is the mechanism by which the alkaloid acts."[3]

Given the lack of response of tremor, Jacobi recommended a combination of harmine with scopolamine.[3] Schuster also noted that "Merck's harmine" or banisterine were only effective for a few weeks. Oral administration of harmine seemed to be ineffective, which was considered a severe commercial drawback by Merck. By 1932, Merck's opinion of harmine was far less optimistic. It was stated that "even if the effects of harmine (. . .) on the symptoms of postencephalitic parkinsonism were not sustained, (. . .) this temporary symptomatic relief, especially on rigidity, often restores inner peace. . .".[3]

Almost 30 years later, in 1958, the Austrian neurologist, Birkmayer, contacted Merck to reassess the use of harmine for Parkinson's disease (PD).[9] However, his request was rejected owing to the known lack of oral efficacy recorded in the company's files.

By 1930, it was generally agreed that hypokinesia, drooling, mood, and sometimes rigidity improved with banisterine and parenteral "Merck's harmine," but that rest tremor sometimes worsened.

Around that time, a German physician, Dr. Halpern, involved himself in self-experimentation and noted a sensation of lightness in his body with increased aggression.[2] After he took 40 mg of harmine by mouth, he reported that "*When lying on a sofa, the light headedness increased to a feeling of floating sensation and the weight of the body was subjectively less. These clinical observations should be compared to the state of levitation frequently reported to occur with the crude drug ayahuasca or caapi . . . . . the author who is normally not belligerent started a fight with a man in the street where he was the one who attacked even though according to the circumstances the prospect for the attacker was unfavourable.*"

Gausebeck compared the effect of harmine with scopolamine in 9 patients with postencepahlitic parkinsonism and 1 patient with paralysis agitans. In 9 of 10 cases, scopolamine therapy was superior irrespective of whether a higher or lower dose (20 vs. 40 mg) of harmine was used. The researcher concluded that the effects observed with harmine injections were short lasting and mild to modest. Furthermore, the oral administration of harmine in combination with scopolamine was not significantly better than scopolamine alone.[10] Dermitzel reported, in 1930, that after 0.2 g of intramuscular injection of harmine, severe intoxication with body cramps, tremor, delirium, and faintness occurred.

In Great Britain, Hill and Worster-Drought treated 38 patients with postencephalitic parkinsonism with "Merck's harmine." The group contained 16 patients with severe, 13 with moderately severe, and 9 with mild signs of parkinsonism, who were all already receiving treatment with SC hyoscine. After hyoscine withdrawal, 19 patients received harmine orally and 19 SC, but none of the patients improved. In fact, all but 1 reported worsening of symptoms, which only improved after hyoscine was restarted.[11] They concluded that, "*Harmine in doses up to 0.04 g given hypodermically has no perceptible objective or subjective effect in ameliorating any of the symptoms presented in the parkinsonian syndrome and is of no value in the treatment of this condition.*"[11] They also suggested that the benefits reported by Rustige et al. were likely to have occurred as a result of suggestion rather than any pharmacological effects of the drug. They could also not replicate the experience of Wilmans and Beringer that the effects of harmine increased with length of treatment. However, they failed to take into account the possibility that abrupt discontinuation of hyoscine could cause severe detrerioration of motor handicap in parkinsonism and could have masked any potential benefits of harmine.

Gunn, a British pharmacologist working in Oxford who had published preliminary positive results with "Merck's harmine," concluded, in 1931, that it was weakly efficacious and inferior to hyoscine.[12]

What 5 years earlier had been heralded as a miracle cure in "Der Kompass" on 1 March 1929 was now being used less and less and usually in combination with atropine or scopolamine.[13] Von Witzleben, who also used the drug, reported that the high hopes for harmine had not been fulfilled.[14] Interestingly, however, on 15 April 1945, Morell asked Stumpfegger to treat Hitler with "Merck's harmine" SC in combination with anticholinergic drops.[15]

The advent of synthetic drugs with pharmacological effects similar to the solanaceous alkaloids finally led to the total abandonment of harmine even in Germany.

More recently, a few patients with PD reported improvement of parkinsonism after the use of ayahuasca (a concoction including *B. caapi* and other plants, some of which contain dimethyltryptamine). Based on the assumption that the beneficial effects were likely to be owing to *B. caapi*, a double-blind, controlled study was carried out in PD. In this study, 30 drug-naïve, de novo PD patients were enrolled and 15 were given 200 mL of *B. caapi* extract, whereas the other half were given 200 mL of placebo matched for taste and color. Side effects were reported in all patients receiving *B. caapi* and included diarrhea, nausea, and in 1 patient transient visual hallucinations. The Unified Parkinson Disease Rating Scale (UPDRS) part III motor scores improved significantly in the active group. Baseline UPDRS scores dropped from 54.4 to 41.4 after 60 minutes, 22.4 after 120 minutes, and 25.6 after 4 hours. However, in all patients, tremor at rest, as well as on action and on posture, worsened.[2] The marked improvement observed in this study is perhaps surprising given that earlier studies reported only mild-to-moderate effect of harmine after oral indigestion. It is, however, impossible to compare the patient groups treated in the 1930s, who used "Merck's harmine," to the study in patients with PD from 2001. "Merck's harmine" contained purified harmine as SC injections whereas the study by Serrano-Dueñas et al. used herbal extracts, which may also contain other active alkaloids.

## Pharmacology of Harmine

Harmine, 7-methoxy-1-methyl-9H-pyrido (3,4-b)indole and harmaline, 4,9-dihydro-7-methoxy-1-methyl-3H-pyrido (3,4-b) indole, and norharmine are found in *P. harmala* and *B. caapi* and are beta carboline alkaloids.[2,16] Though harmaline is almost



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exclusively found in *P. harmala* seeds, harmine can be extracted from both the seeds and roots.[17] The pharmacological effects of harmine have been attributed mainly to its central monoamine oxidase (MAO) inhibitory properties, but in vivo and rodent studies have shown that extracts of *B. caapi* and also *P. harmala* lead to striatal dopamine release.[18–20]

Harmine is also a *N*-methyl-D-aspartate (NMDA) receptor antagonist.[21] Some researchers speculated that the rapid improvement observed in PD patients might be owing to these antiglutamatergic effects.[2]

Rodent studies have shown that harmine can also reduce cerebral infarct volume and neuronal cell death owing to upregulation of glutamate transporter 1, which attenuates excessive and neurotoxic glutamate levels, leading to speculation that harmine might also possess neuroprotective properties.[22] Harmine is a selective inhibitor of the DYRK1A protein kinase, a molecule necessary for neurodevelopment,[23,24] and has been shown to support survival of dopaminergic neurons in MPTP-treated mice.[25]

## Use of MAO Inhibitors in PD

In 1958, Udenfriend et al. demonstrated that harmine was a nonselective MAO inhibitor.[26] In 1968, two subtypes of MAO inhibition type A and B were identified.[27] MAO-A inhibition has been shown to significantly shorten latency to onset and increase the duration of motor responses after a single dose of levodopa. Furthermore, and in contrast to MAO-B inhibition, MAO-A is also present within presynaptic dopaminergic terminals.[28,29] In 1964, harmine was shown to antagonize reserpine-induced parkinsonism.

Nonselective monoamine inhibitors were reported to have antiparkinsonian effects in the early 1960s[30] and to markedly enhance the therapeutic effects of low doses of L-dopa.[30,31] Subsequent research, however, confirmed that they could not be used safely with L-dopa because of potentially dangerous hypertensive effects.[32] The so-called "cheese effect," an increase of blood pressure after consumption of tyramine-containing foods, was also observed in patients treated with clorgyline, a unselective and irreversible MAO type A inhibitor.[33] Moclobemide is a reversible type A inhibitor that is free of cheese effects and has been reported in studies to have mild antiparkinsonian effects.[28,29] Although moclobemide can also alleviate depression in PD,[34] the effects of MAO-A inhibitors have not been well studied. Caution is required when moclobene is combined with antidepressants given that it may cause serotonin syndrome,[35] which would likely be a limitation of harmine in modern clinical practice.

In contrast, type B MAO inhibitors have been extensively investigated. In the mid-1970s, it was shown that selegiline could modestly prolong the motor response of L-dopa, have weak antiparkinsonian effects when used as monotherapy, and can be used safely with L-dopa without dietaryl tyramine.[36] Interestingly, however, studies have shown that selegiline is not a selective MAO- type B inhibitor, but acts at higher doses also as an MAO-A inhibitor.[37]

In relation to the responses reported with harmine, it is also of interest that the data sheet for selegiline states that doses beyond 10 mg can worsen tremor. Many opinion leaders have also observed that both selegiline and the more recently marketed type B MAO inhibitor, rasagiline, can spectacularly improve some patients for many months, whereas other patients do not respond at all or notice worsening of tremor similar to the original observations with harmine.

## Harmine and Tremor

Harmine triggers an 8- to 14-Hz acute, but temporary, postural and action tremor in rodents (see Video 2), cats, and monkeys. Whole-body tremor is dose dependent and develops within minutes after an SC injection and can last up to several hours.[38] In healthy volunteers, high doses of *B. caapi* can induce a transient coarse tremor.[39] Acute harmine intoxication leads to tremor, hypersalivation, agitation, and subsequently to paralysis, tonic clonic seizures, and eventually to death,[40] whereas repeated daily administration of higher harmaline doses result in tolerance and a progessive diminution of tremor.[38]

The tremor induced by harmine is believed to be a result of activation of the medial and dorsal accessory inferior olivary nuclei and the cerebellum. High doses of harmine can cause Purkinje cell loss in rodents.[41] There are several similarities in phenomenology of harmine-induced tremor and essential tremor (ET). For example, citalopram, imipramine, and caffeine worsen both harmaline and ET. Approximately half of the drugs that suppress harmine-induced tremor also supress ET. Alcohol, primidone, and β-blockers can suppress harmaline-induced tremor,[42] but may exacerbate neural damage.[38] Although slowness of movements has been observed in harmine-treated rodents, it is likely that this phenomenon is secondary to tremor and does not reflect true bradykinesia.[43] Finally, elevated harmane levels, of which harmine is one of its metabolites, has been found in patients with ET. Although the exact putative mechanisms of harmane elevation is unclear, it may involve genetic susceptibility of patients, increased dietary intake, or a combination of both.[44]

## Harmine and Depression

Harmine interacts with serotonin receptor 2A and has been shown to have antidepressant-like effects in rodent models. Acute and chronic doses of harmine increased swimming and climbing time and reduced immobility time in a forced swimming test in rats.[45,46] Furthermore, harmine increases brain-derived neurotrophic factor (BDNF) in rat hippocampus.[45,46] In humans, decreased BDNF levels have been associated with major depression. Furthermore, MAO-A inhibitors reduce the breakdown of serotonin and noradrenaline and are used to treat depression.[46,47]

Despite the considerable evidence for antidepressant effects in animal models, harmine was never used as an antidepressant in humans. It was, however, already mentioned, in 1930, that it may be useful in patients with catatonic schizophrenia and has



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recently been proposed again as a potential treatment option for psychosis.

## Discarded Therapies

Many of the treatments and nostrums used to treat PD in the late 19th century and early 20th century have now been discarded on the grounds of lack of proven efficacy. These include calabar beans, Bulgarian belladonna extract, monkey glands, and parathyroid extract. Anticholinergic drugs despite the lack of modern trial evidence were, on the other hand, judged to be efficacious.[48] Others, such as Indian hemp, opium, and amphetamines, although no longer used now, have known pharmacological actions that would make them putative candidates for further trials.

A salutary example of a drug that was forgotten to the detriment of many patients with PD is apomorphine.

In 1951, apomorphine was shown to improve decerebrate rigidity and on empirical grounds was used by Schwab et al. to treat PD patients.[49] However, the beneficial effects were noted to be brief, and side effects such as nausea and vomiting were frequently observed. Oral doses of apomorphine were unsuccessful because of rapid first-pass metabolism. The fact that apomorphine was a potent dopamine receptor agonist and that striatal dopamine deficiency occurred in PD had not yet been discovered,[50] but even in 1978, when these facts were long established, it was stated that, "*unfortunately, apomorphine is of no practical use in the treatment of Parkinson's disease because its beneficial effect is of short duration (about 1 hour) and accompanied by side effects. . . .*".[51]

In the 1980s, the development of ambulatory pump delivery systems and the marketing of domperidone, a peripheral dopamine antagonist, led to a reinvestigation of apomorphine with gratifying results. SC waking-day apomorphine is now an established therapy for refractory motor fluctuations, with efficacy comparable to that observed with L-dopa.[50]

The first human studies with L-dopa, the gold-standard therapy in PD, also reported conflicting results. In 1960, Sano reported the effect of L-dopa in PD patients. He administered 200 mg of L-dopa intravenously and observed a marked reduction of rigidity and tremor 15 to 30 minutes after injection. However, he noted that "the effects were transient and the patients returned to their pre-treatment status within a few minutes." Therefore, he concluded that "that treatment with dopa had no practical therapeutic value."[52] Furthermore, McGeer, in 1964, reported that only 2 of 10 patients improved after receiving L-dopa therapy and concluded "that dopa has little to offer as a therapeutic agent in the treatment of parkinsonism."[53]

## Conclusions

Harmine has an interesting pharmacological profile with selective MAO type A inhibition, serotonin affinity, NMDA receptor antagonism, and possible antioxidative, as well as neuroprotective, properties and may also cause direct striatal dopamine release.

The view that only selective type B MAO inhibitors are likely to be efficacious in PD is not backed up by the available data. If confirmed, harmine's fast mode of action could be a valuable expansion to currently available therapy in PD. Though it seems improbable that harmine is a potent antiparkinsonian agent, it could be as efficacious as the commerically available selective type B MAO inhibitors. Furthermore, based on the historical trials and recent preclincal and clinical studies, safinamide, a synthetic molecule that has been granted a license for PD recently, has a pharmacological profile that resembles *B. caapi* with the exception that it is considered to be a MAO type B inhibitor. *Banisteriopsis caapi* extracts may be superior to extracts of *P. harmala* and are worthy of further controlled trials.[2]

## Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

A.D.: 1A, 1B, 1C, 3A
S.B.-R.: 1B, 3B
W.P.: 1B, 3B
A.J.L.: 1A, 1B, 3B

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## Supporting Information

Videos accompanying this article are available in the supporting information here.

Both videos are recorded by Willmans and Beringer in Heidelberg in 1929 and presented at the Deutsche Pharmakologische Gesellschaft in Muenster. Source: Merck Corporate History, Darmstadt, Germany.

**Video 1.** Intermittent action tremor and unsteadiness after low dose of harmine injection (dose unknown). Sequence 2 (after higher doses of harmine injections of unknown dose): violent jerking and severe unsteadiness. Sequence 3: rest tremor on trunk with akinesia of all four limbs.

**Video 2.** Possibly from 1929; done by Willmans and Beringer in Heidelberg and presented at the Deutsche Pharmakologische Gesellschaft in Muenster. Source: Merck Corporate History, Darmstadt, Germany.

Patient 1: Female patient after encephalitis with "vigorous eyelid closure tics." Bilateral vigorous eyelid closure in combination with oromandibular dystonia. Spasms are short lasting; in between attacks, there is no sign of dystonia. During distraction (injection), short spasms affecting mainly the left side. Symptoms disappear after injection. Interval between injection and improvement unknown. Likely, placebo response in a patient with a nonorganic movement disorder.

Patient 2: Male patient with severe left-sided akinetic rigid parkinsonism and bucco-linguo-masticatory symptoms. Stooped posture, arising from chair normal, intermittent dragging of left leg. Tremor on left upper limb while walking with no arm swing bilaterally. Stride length slightly reduced. Right lower limb tremor while sitting (more pronounced during injection). Interval between injection and retesting unknown. Significant improvement after injection, with relaxed facial expression. Posture still slightly stooped, intermittent bucco-linguo-masticatory symptoms, particularly when walking backward. No difficulty turning, gait with normal stride length, slight reduction of arm swing bilaterally. Mild intermittent tremor in left upper limb when walking.


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